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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,044	07/21/2003	Andrew J. Murphy	REG 780BZ	6377

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REGENERON PHARMACEUTICALS, INC
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EXAMINER

SGAGIAS, MAGDALENE K

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/624,044

Applicant(s)

MURPHY ET AL.

Examiner

Magdalene K. Sgagias

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 May 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44-47 and 53 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44-47 and 53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>7/21/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 44-47 have been amended. New claim 53 has been added. Claims 44-47 and 53 are pending and under consideration.

Response to Arguments

Applicant's arguments, see page 6 of Applicant's response, filed on 05/30/06, with respect to formal objections have been considered and are persuasive. The specification has been amended and hyperlinks have been removed. Claim 52 has been canceled. Therefore, objections have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicant's arguments, see page 6 of Applicant's response, filed 05/30/06 with respect to the rejection of claims 44-47 under 35 U.S.C. & 112, first paragraph, for lack of enablement have been fully considered and are persuasive. It is noted that claims 35-39 are withdrawn as claims are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicant's arguments, see pages 6-7 of Applicant's response, filed 05/30/06 with respect to the rejection of claims 44-47 under 35 U.S.C. & 112, second paragraph, as indefinite have been fully considered and are persuasive. It is noted that claimed language has been amended to embrace a transgenic mouse containing an endogenous gene locus that has been replaced with an exogenous gene locus. Therefore, rejection of claims 44-47 has been withdrawn.

Applicant's arguments see pages 7-8, filed 05/30/06 with respect to the rejection under 35 U.S.C. & 102(e) have been fully considered but they are not persuasive. Applicants argue that the present claims are distinguished from the cited patent in numerous respects. First, the transgenic mice discussed by the examiner are relevant only as a means for generating hybridomas that will provide the subject for antibody modification. By contrast, in the present claims the transgenic mice themselves are modified to produce antibodies. Second, the modifications performed in the cited patent on hybridomas are of the rearranged genes encoded by the hybridomas. Such is apparent from the purpose described for modifying variable region (i.e., changing specificity or affinity). Antibody genes do not encode an antibody having any specificity or affinity until they have undergone rearrangement. By contrast the present claims

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specify hybrid loci that rearrange during B-cell development. Third, the nature of the modification proposed in the patent is different than that specified in the present claims. The patent proposes changing the affinity or specificity of variable regions not replacing a mouse variable region with a locus, and particularly not such that the human locus is thereby linked to a mouse constant region locus (p7-8).

In response this is not found persuasive because the claimed invention encompass transgenic mice wherein human Ig region loci replace mouse endogenous loci. As such, the rejection of claims 44-47 is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 46 is directed to a transgenic mouse wherein the endogenous immunoglobulin variable region gene locus has been replaced with a homologous or orthologous human variable region gene locus.

The specification has contemplated a transgenic mouse whose genome comprises mouse wherein the endogenous immunoglobulin variable region gene locus has been replaced with a homologous or orthologous human variable region gene locus (p 20). The specification however, has not described any homologous or orthologous human variable region gene locus encompassed by the claims. The instant specification has contemplated the creation of the transgenic mice encompassed by the claims. However, the creation of such is merely a goal of the instant specification, as the claimed mice were not actually made. The evidence of record does not suggest predictability of the existence of the genus of transgenic mice encompassed by the claims. As such the transgenic mice encompassed by the claims and their corresponding phenotypes have not been described by the instant specification.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the

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inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). However, it would appear that at the time the instant application was filed Applicants were not in possession of the transgenic mice encompassed by the claims, as the instant specification has not reduced to practice such. The skilled artisan cannot envision the detailed chemical structure of the transgenic mice encompassed by the instant claims, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of creating a transgenic mouse. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

The skilled artisan would not recognize that applicant was in possession of the necessary common features or attributes possessed by the genus of transgenic mouse embraced by the claims as such has not been reduced to practice by the instant specification. As such it would appear from the evidence of record that Applicant was not in possession of the genus of transgenic mouse encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 44-47 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by **Lonberg et al**, (U.S. 5,877,397, patented March 2, 1999).

Lonberg et al, teach transgenic mice comprising human Ig genes that are introduced into the mouse Ig locus by replacing mouse heavy and light immunoglobulin loci directly with fragments of the human heavy and light chain loci using homologous recombination (columns 31-74). Lonberg et al, teach genomic heavy chain human Ig transgene (column 31, example 1). Lonberg et al, teach genomic kappa light human Ig transgene formed by in vivo homologous recombination (column 32, second example). Lonberg et al, teaches identification of functionally rearranged variable region sequences in transgenic B cells (column 70, example 17).

Thus, claims 44-47 and 53 are anticipated.

Claims 44-47 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by **Kucherlapati et al**, U.S. Patent 6,114,598, patented September 5, 2000.

Kucherlapati et al, teach transgenic mice comprising human Ig genes that are introduced into the mouse Ig locus by replacing mouse heavy and light immunoglobulin

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loci directly with fragments of the human heavy and light chain loci using homologous recombination (column 38, lines 16019). Kucherlapati et al, teach replacing human sequences include 100 kb fragment of the human heavy chain region (column 38, lines 23-26). Kucherlapati et al, teach transgenic mice comprising human Ig genes that are introduced into the mouse Ig locus by replacing the constant as well as the J region of the kappa locus and replace it with three elements through homologous recombination using regions of homology flanking the constant region (column 25, lines 16-23). Kucherlapati et al, teach transgenic mice comprising human Ig genes that are introduced into the mouse Ig locus by replacing the kappa light chain constant (Ck) region (column 22, lines 1-10). Kucherlapati et al, teach transgenic mice producing human monoclonal antibodies in response to immunization (column 39 and 40).

Thus, claims 44-47 and 53 are anticipated.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

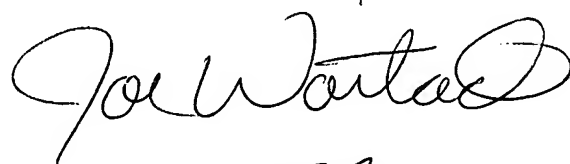
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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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